Drug Class Review
on
Triptans

Update #4: Preliminary Scan Report

March 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #3 Final Report was completed in November of 2005.

Scope and Key Questions

Key Questions

1. What is the comparative effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?

2. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?

3. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Population

Adult patients with migraine. Definition of migraine must be explicit, to exclude other types of headache (e.g. tension headache). Any level of migraine (mild, moderate, severe) and with or without aura will be included.

Interventions (oral, nasal and injectable)

Almotriptan (Axert)
Eletriptan (Relpax)
Frovatriptan (Frova)
Naratriptan HCL (Amerge)
Rizatriptan (Maxalt)
Rizatriptan orally disintegrating tablet (Maxalt-MLT)
Sumatriptan (Imitrex)
Zolmitriptan (Zomig)

Zolmitriptan orally disintegrating tablet (Zomig-ZMT)

Effectiveness outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (e.g., change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain free, sustained response, sustained pain free, significant response, rescue (use of rescue medications), relapse (reappearance of any degree of symptoms within 48 hours) after response or becoming pain free, time to relief and relief of associated symptoms.

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects (e.g., CNS effects, chest tightness)

Study designs

1. For effectiveness, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
2. For safety, the study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (November 2005 to March 2007). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 51 potentially relevant citations. Of those, there are 18 new potentially relevant controlled clinical trials (Appendix A).

New Drugs

None

New Indications

None

New Safety Alerts

Sumatriptan
Date: 2/2006
Source: FDA
Events Observed in Association with the administration of Imitrex Injection: Eye: Vision Alterations; Gastrointestinal: Abdominal discomfort; Dysphagia; Musculoskeletal: Muscle Cramps; Neurological: Anxiety

All Triptans
Date: 7/2006
Source: FDA
FDA notified of new safety information regarding taking medications used to treat migraine headaches (triptans) together with certain types of antidepressant and mood disorder medications (selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs). A life-threatening condition called serotonin syndrome may occur when triptans are used together with a SSRI or a SNRI. Serotonin syndrome occurs when the body has too much of a chemical found in the nervous system (serotonin). Each of the above medications (triptans, SSRIs, and SNRIs), cause an increase in serotonin levels. Symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea.

APPENDIX A

Brandes, J. L., D. Kudrow, et al. (2005). "Eletriptan in the early treatment of acute migraine: influence of pain intensity and time of dosing." Cephalalgia **25**(9): 735-42.

This double-blind, placebo-controlled study was designed to evaluate the efficacy and tolerability of early treatment of a single migraine attack, when headache pain was mild, with two doses (20 mg and 40 mg) of eletriptan. Patients (N = 613; female 79%; mean age 39 years) meeting International Headache Society criteria for migraine were encouraged, but not required, to utilize early treatment, thus providing an opportunity to assess the relative contribution to efficacy of pain severity and timing of dose. For the total patient sample (mild-to-severe headaches), 2-h pain-free rates were significantly higher than placebo (22%) on both eletriptan 20 mg (35%; P < 0.01) and eletriptan 40 mg (47%; P < 0.0001). For the cohort of patients who treated their headache when the pain intensity was mild, the 2-h pain-free rate on eletriptan 40 mg was 68% compared with 25% on placebo (P < 0.0001). Pain intensity at the time of taking eletriptan appeared to influence outcome more than the timing of the dose relative to headache onset. Eletriptan was well-tolerated, with adverse event rates similar to placebo when mild headaches were treated.

Cady, R., V. Martin, et al. (2006). "Efficacy of Rizatriptan 10 mg administered early in a migraine attack." Headache **46**(6): 914-24.

OBJECTIVE: To determine if administration of rizatriptan 10 mg is superior to placebo for the early treatment of acute migraine, while the pain is mild. BACKGROUND: Past studies have suggested that treatment outcomes can be improved if a triptan is administered early in the time course of a migraine attack. METHODS: Two randomized, parallel, placebo-controlled, double-blind studies. TAME (Treat A Migraine Early)1 was conducted at 46 centers in the United States; TAME2, at 48 centers in the United States. Totally, 1030 adult patients with at least a 6-month history of migraine were studied. Patients were instructed to treat within 1 hour of migraine onset, while pain was mild. Patients maintained a headache diary in which they rated their levels of pain and disability, and recorded other symptoms of migraine. Primary endpoints were pain freedom at 2 hours and sustained pain freedom at 24 hours post-dose. RESULTS: In TAME1, 57.3% versus 31.1% of patients reported pain freedom at 2 hours post-dose and 42.6% versus 23.2% reported 24-hour sustained pain freedom with rizatriptan versus placebo, respectively (P < .001 for both). In TAME2, 58.9% versus 31.1% of patients reported pain freedom at 2 hours post-dose and 48.0% versus 24.6% reported 24-hour sustained pain freedom with rizatriptan versus placebo, respectively (P < .001 for both). All other efficacy endpoints favored rizatriptan. Repeat doses of the medicine were not allowed; patients may have delayed treatment; non-migraine headaches may have been treated. CONCLUSIONS: Rizatriptan 10 mg was superior to placebo when treating migraine early, while pain is mild, as measured by pain freedom at 2 hours and 24-hour sustained pain freedom.

Cittadini, E., A. May, et al. (2006). "Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study." Archives of Neurology **63**(11): 1537-42.

BACKGROUND: Cluster headache is a form of primary headache in which attacks are rapid in onset with very severe pain. The mainstays of acute therapy are inhaled oxygen and sumatriptan succinate injection. OBJECTIVE: To evaluate zolmitriptan nasal spray in the acute treatment of cluster headache. METHODS: Ninety-two patients, aged 40 +/- 10 years (mean +/- SD) (80 men and 12 women), with International Headache Society-defined cluster headache were randomized into a placebo-controlled, double-blind crossover study. Patients treated 3 headache attacks using placebo for 1 attack, 5 mg of zolmitriptan nasal spray (ZNS5) for 1 attack, and 10 mg of zolmitriptan nasal spray for 1 attack. The primary end point was headache relief at 30 minutes, defined as reduction from moderate, severe, or very severe pain to no or mild pain. The study was

approved by the appropriate ethics committees. RESULTS: Sixty-nine patients were available for an intention-to-treat analysis. The 30-minute headache relief rates were placebo, 21%; ZNS5, 40%; and ZNS10, 62%. Modeling the response as a binary outcome, the Wald test was significant for the overall regression (chi(2)(1) = 29.4; P<.001), with both ZNS5 and ZNS10 giving significant effects against placebo. Headache relief rates for patients with episodic cluster headache were 30% for placebo, 47% for ZNS5, and 80% for ZNS10, while corresponding rates for patients with chronic cluster headache were 14%, 28%, and 36%, respectively. Zolmitriptan was also well tolerated. CONCLUSION: Five-milligram and 10-mg doses of zolmitriptan intranasal spray are effective within 30 minutes and well tolerated in the treatment of acute cluster headache. Trial Registration controlled-trials.com Identifier ISCRTN27362692.

Diener, H.-C. (2005). "Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: a double-blind, randomized, placebo-controlled study in patients controlled study in patients with previous poor response to sumatriptan 50 mg." Current Medical Research & Opinion **21**(10): 1603-10.

BACKGROUND: Triptans are not identical and migraine sufferers respond differently to different triptans. Few studies have evaluated the efficacy of switching triptans in migraine patients who have shown poor response to another agent. OBJECTIVE: To investigate the efficacy and tolerability of almotriptan 12.5 mg in patients who did not achieve 2-h pain relief with sumatriptan 50 mg. METHODS: This double-blind, placebo-controlled study recruited patients with IHS-defined migraine and at least 2 previous unsatisfactory responses to sumatriptan. Those who did not achieve pain relief (moderate or severe pain decreasing to mild or no pain) 2 h after taking oral sumatriptan 50 mg on an open-label basis for the treatment of their first migraine attack during this trial (Attack 1) were randomized to receive either oral almotriptan 12.5 mg or placebo for the treatment of their next migraine attack (Attack 2). RESULTS: Of 302 patients receiving sumatriptan 50 mg for the treatment of their first migraine attack, 221 (73%) did not achieve 2-h pain relief and were randomized to almotriptan 12.5 mg or placebo for the treatment of Attack 2. The majority (70%) of randomized patients treating their headache in Attack 2 reported severe pain at baseline characterizing this as a difficult-to-treat population. In the intent-to-treat population (n = 198), significantly more patients in the almotriptan group compared with the placebo group achieved 2-h complete relief (free from pain and migraine-associated symptoms) at 2 h (17.1% vs. 4.4%; $p < 0.05$) and sustained pain free (20.9% vs. 9.0%; $p < 0.05$). Adverse events of mild-to-moderate intensity occurred in 7.1% of patients in the almotriptan group compared to 5.1% in the placebo group (not statistically different). CONCLUSION: Almotriptan is more effective than placebo and similarly well-tolerated for the acute treatment of migraine in patients who responded poorly to oral sumatriptan.

Diener, H.-C., A. Gendolla, et al. (2005). "Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial." Headache **45**(7): 874-82.

OBJECTIVE: To investigate the efficacy and tolerability of almotriptan 12.5 mg in migraine patients who respond poorly to sumatriptan 50 mg. BACKGROUND: Poor response to sumatriptan therapy for acute migraine attacks has been documented in the literature, but few controlled trials have investigated the efficacy of an alternative triptan in this subgroup of patients. METHODS: Patients with an International Headache Society diagnosis of migraine who self-described as experiencing at least two unsatisfactory responses to sumatriptan treated their first migraine attack with open-label sumatriptan 50 mg. Patients who did not achieve 2-hour pain relief (improvement of headache from moderate/severe to mild/no headache) were then randomized to treat their second attack with almotriptan 12.5 mg or placebo under double-blind conditions. RESULTS: In the first attack, 221 of 302 participants (73%) did not achieve 2-hour pain relief with sumatriptan and were randomized to treatment of their second attack with

almotriptan 12.5 mg or placebo. Of the 198 sumatriptan nonresponders who treated their second attack (99 almotriptan; 99 placebo), 70% had severe headache pain at baseline. Two-hour pain-relief rates were significantly higher with almotriptan compared to placebo (47.5% vs 23.2%; P<.001). A significant treatment effect for almotriptan was also seen in pain-free rates at 2 hours (33.3% vs 14.1%; P<.005) and sustained freedom from pain (20.9% vs 9.0%; P<.05). In the second attack, 7.1% of patients in the almotriptan group experienced adverse events compared to 5.1% in the placebo group (P=.77). CONCLUSIONS: Almotriptan 12.5 mg is an effective and well-tolerated alternative for patients who respond poorly to sumatriptan 50 mg. A poor response to one triptan does not predict a poor response to other agents in that class.

Friedman, B. W., M. Hochberg, et al. (2006). "A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines." Headache **46**(6): 934-41.

BACKGROUND: Although various classes of medication are used to treat acute migraine in the emergency department (ED), no treatment offers complete pain relief without side effects or recurrence of headache. Consequently, even though several antiemetic medications as well as SQ sumatriptan have demonstrated efficacy and tolerability for the ED treatment of migraine, there remains a need for more effective parenteral therapies. Open-label studies suggest that the combination of trimethobenzamide and diphenhydramine (TMB/DPH) may provide effective relief in a high proportion of migraineurs. OBJECTIVE: To test the hypothesis that ED patients with acute migraine, given intramuscular TMB/DPH, would have a larger reduction in their pain scores than patients given SQ sumatriptan. METHODS: This was an ED-based, randomized, double-blind, "double-dummy" clinical trial comparing 2 parenteral treatments for acute migraine headaches. Subjects received a combination of TMB 200 mg and DPH 25 mg as a single intramuscular injection or 6 mg of SQ sumatriptan. Pain scores, disability scores, associated symptoms, and adverse effects were assessed for 2 hours in the ED and by telephone 24 hours after medication administration. The primary outcome was the between-group difference in reduction of pain intensity as measured by a validated numerical rating scale 2 hours after medication administration. This study was designed to detect superiority of TMB/DPH; therefore, a 1-tailed t-test was used. An interim analysis was planned to terminate the trial if predetermined endpoints in the primary outcome variable were reached. RESULTS: The trial was stopped by the data monitoring committee after 40 subjects were enrolled because a substantial benefit in the primary outcome was found favoring sumatriptan. Baseline pain scores were comparable between the 2 groups. By 2 hours, sumatriptan subjects had improved by a mean of 6.1 and the TMB/DPH subjects had improved by a mean of 4.4 (95% CI for difference of 1.7: -0.1 to 3.4). By 24 hours after medication administration, sumatriptan subjects had a mean improvement from baseline of 4.9 as compared to 5.3 for TMB (95% CI for difference of -0.4: -2.4 to 1.6). The need for rescue medication was comparable between the groups. No serious or frequent adverse effects were noted in either group. CONCLUSIONS: SQ sumatriptan is probably superior to TMB/DPH for treating the pain of acute migraine at 2 hours. However, TMB/DPH was well-tolerated, efficacious, and relieved pain comparably to sumatriptan at 24 hours. TMB/DPH might have a role in select populations in which sumatriptan is contraindicated or likely to be ineffective.

Gawel, M., J. Aschoff, et al. (2005). "Treatment satisfaction with zolmitriptan nasal spray for migraine in a real life setting: results from phase two of the REALIZE study." Journal of Headache & Pain **6**(5): 405-11.

In phase one of the REALIZE study, zolmitriptan nasal spray demonstrated a significant headache response from 10 min post-dose and total symptom relief from 30 min post-dose. The objective of phase two was to investigate patients' dosing patterns, satisfaction and preference following open-label treatment with the nasal spray. Up to 3 attacks were treated. The ITT population consisted of 851 patients. The median time from onset of symptoms to treatment was 1 h 15 min (primary endpoint). Most patients reported being satisfied or very satisfied with

zolmitriptan nasal spray (75.7%). Furthermore, the majority of patients would be willing to use zolmitriptan nasal spray in the future (59.8%) and preferred zolmitriptan nasal spray over previous therapies (57.8%). Zolmitriptan nasal spray was well tolerated. Most patients were satisfied with zolmitriptan nasal spray, were willing to continue using it and preferred it to previous therapies.

Goldstein, J., S. D. Silberstein, et al. (2005). "Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial.[see comment]." Headache **45**(8): 973-82.

OBJECTIVE: To address the need for a rigorous, direct comparison of prescription and over-the-counter (OTC) migraine drugs and to expand the database on early treatment of migraine. BACKGROUND: Most people who experience migraine use OTC medications to treat their symptoms, but no head-to-head clinical trials comparing these agents with prescription migraine therapies have been published. In addition, even though most migraineurs treat early in the attack, few studies have been conducted to reflect this treatment pattern. METHODS: We compared a combination of nonprescription migraine medication (acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg) with a prescription migraine product (50 mg sumatriptan) in a randomized, controlled clinical trial in which subjects treated at the first sign of a migraine attack. Subjects who reported vomiting during more than 20% of migraine episodes or who required bedrest during more than 50% of migraine episodes were excluded from the study. Of the 188 subjects randomized, 171 took study medication and were included in the analysis. CONCLUSION: The combination of acetaminophen, aspirin, and caffeine was significantly more effective ($P > .05$) than sumatriptan in the early treatment of migraine, as shown by superiority in summed pain intensity difference, pain relief, pain intensity difference, response, sustained response, relief of associated symptoms, use of rescue medication, disability relief, and global assessments of effectiveness. An additional, larger clinical trial is needed to confirm these results.

Gregor, N., C. Schlesiger, et al. (2005). "Treatment of cluster headache attacks with less than 6 mg subcutaneous sumatriptan." Headache **45**(8): 1069-72.

BACKGROUND: Subcutaneous (SQ) sumatriptan 6 mg is effective in the treatment of acute cluster headache attacks. However, patients sometimes benefit from a dose less than 6 mg. OBJECTIVE: Therefore, we designed a prospective open study to evaluate how many patients benefit from a dose less than 6 mg SQ sumatriptan. METHODS: We enrolled 81 consecutive patients with cluster headache and recorded their use of SQ sumatriptan and oxygen. Patients regularly using SQ sumatriptan 6 mg were advised to treat attacks with doses less than 6 mg and with oxygen. Efficacy and side effects of the different treatment options (6 mg, 3 mg, 2 mg, and oxygen) were evaluated. RESULTS: As a result, 74% of the patients using SQ sumatriptan 3 mg showed efficacy and 89% reported efficacy after 2 mg. Seventy-nine percent reported side effects after the use of SQ sumatriptan 6 mg (29% severe side effects). After the use of 2 mg SQ sumatriptan, only 50% of the patients reported side effects, none of these were classified as severe. Patients' preference was 41% for 6 mg sumatriptan, 28% for doses less than 6 mg, and 31% for oxygen. CONCLUSIONS: We conclude that sumatriptan in doses less than 6 mg can be effective in the acute treatment of cluster headache attacks. We suggest that patients should have experience in their individual efficacy of sumatriptan doses less than 6 mg.

Jelinski, S. E., W. J. Becker, et al. (2006). "Pain free efficacy of sumatriptan in the early treatment of migraine." Canadian Journal of Neurological Sciences **33**(1): 73-9.

BACKGROUND: There is evidence that headache response rates may be higher if triptans are used early when a migraine attack is still mild, as compared to when it is treated after pain has reached moderate or severe intensity. METHODS: In this randomized, double blind, placebo controlled, parallel group clinical trial, 361 patients took either placebo, sumatriptan 50 mg, or

sumatriptan 100 mg in a single attack study. The primary outcome measure was pain-free status at two hours. RESULTS: In the intention to treat group, two hour pain free rates were 16%, 40%, and 50% in the placebo group, sumatriptan 50 mg group, and the sumatriptan 100 mg group respectively ($p < 0.001$, active treatment groups vs. placebo). CONCLUSIONS: Both sumatriptan 50 mg and 100 mg were significantly superior to placebo for the pain-free end point at two hours. The pain-free response rates in this trial where sumatriptan was taken while the headache was still mild were generally higher than in older clinical trials where headache was treated after reaching a moderate or severe intensity.

Lainez, M. J. A., S. Evers, et al. (2006). "Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine." Cephalalgia **26**(3): 246-56.

Preference is a composite, patient-oriented endpoint incorporating efficacy, tolerability, formulation, and convenience of medications. The objective of this study was to compare patient preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. In this multicentre, open-label, two-period, crossover study, out-patients were randomly assigned to treat the first of two moderate to severe migraines with rizatriptan or eletriptan and the second with the alternate therapy. Patients completed diary assessments at baseline and up to 24 h after taking study medication. At the last visit, patients completed a psychometrically validated preference questionnaire. A total of 372 patients (mean age 38 years, 85% female) treated two migraine attacks, and 342 patients (92%) expressed a preference for treatment. Significantly more ($P < or = 0.001$) patients preferred rizatriptan 10-mg wafer [61.1%; 95% confidence interval (CI) 55.7, 66.3] to eletriptan 40-mg tablet (38.9%; 95% CI 33.7, 44.3). The most common reason given for preference of either treatment was speed of headache relief. At 2 h, 80% and 69% of patients reported that rizatriptan and eletriptan, respectively, was convenient or very convenient to take (mean convenience score 1.99 vs. 2.31, respectively; $P < or = 0.001$). Both triptans were well tolerated. In this head-to-head study designed to evaluate global patient preference, significantly more patients preferred the rizatriptan 10-mg wafer to the eletriptan 40-mg tablet for acute treatment of migraine. The single most important reason for preference was speed of relief, consistent with results from previous preference studies.

Martin, V. T., E. Loder, et al. (2005). "Eletriptan treatment of migraine in patients switching from barbiturate-containing analgesics: results from a multiple-attack study." Cephalalgia **25**(9): 726-34.

The aim of this study was to examine efficacy and tolerability of eletriptan in patients switched from barbiturate-containing combinations (Fiorinal), Fioricet. Migraineurs (n = 160) meeting IHS criteria, with unsatisfactory response in the past year to butalbital-containing combinations, treated up to 16 attacks over 3 months with eletriptan 40 mg. Assessments included headache response and pain-free rates and functional impairment at baseline and 2 h postdose, and global ratings of treatment satisfaction at 24 h. At 2 h postdose, average headache response and pain-free rates were 71% (95% CI, 69-74%) and 37% (95% CI, 35-40%), respectively; 68.5% of patients (95% CI, 65-72%) reported functional response. Within-patient analysis found no efficacy diminution over time (no tolerance). Average headache recurrence rate was 20% (95% CI, 18-23%). Eletriptan was well-tolerated; 6 (3.7%) patients discontinued due to adverse events. There were no serious treatment-related adverse events. We conclude that in poor responders to butalbital-caffeine combinations, switching to eletriptan 40 mg was well-tolerated and efficacious.

Massiou, H., A. Pradalier, et al. (2006). "Evaluation of efficacy, tolerability, and treatment satisfaction with almotriptan in 3 consecutive migraine attacks. The migraine--satisfaction with treatment: reality with Almogran study." European Neurology **55**(4): 198-203.

The objective of the open-label, multicenter Migraine--Satisfaction with Treatment: Reality with Almogran study was to assess efficacy, tolerability, and satisfaction with almotriptan 12.5 mg

among migraineurs who were not achieving adequate results with their current acute therapy. Data from 434 patients (342 evaluable), were obtained for 929 attacks by 154 neurologists in France. Using a questionnaire developed by the National Agency for Accreditation and Evaluation in Health (ANAES), almotriptan was associated with an increased proportion of patients experiencing significant relief at 2 h (69.3 vs. 26.6%), tolerating the medication well (91.2 vs. 76.0%), able to resume activities (70.5 vs. 24.9%), and taking only 1 dose (59.4 vs. 28.1%) compared with previous therapies. At 2 h, headache pain had disappeared in 33.4% of attacks and was mild in 26.9%. Recurrence rate was 28.4% and rescue analgesics were used in 20.9% of attacks. The rate of adverse event-related discontinuations was 2.6%. The proportion of patients who were very satisfied/satisfied overall with almotriptan treatment was 69%. Almotriptan 12.5 mg was effective, well-tolerated and associated with a high rate of treatment satisfaction in patients whose previous acute migraine therapy was inadequate according to the ANAES recommendations.

Pascual, J., C. Garcia-Monco, et al. (2005). "Rizatriptan 10-mg wafer versus usual nontriptan therapy for migraine: analysis of return to function and patient preference." Headache **45**(9): 1140-50.

BACKGROUND: More than half of patients with migraine suffer moderate to severe functional disability during migraine attacks. OBJECTIVE: To compare effects on functional disability at 2 hours after treating a migraine with rizatriptan 10-mg wafer versus usual nontriptan therapy for triptan-naive patients with migraine. DESIGN: Open-label, prospective, two-attack study conducted at 111 neurology clinics. METHODS: Adult patients with migraine treated two migraine attacks, the first with their usual nontriptan therapy (nonsteroidal anti-inflammatory drugs, 57%; analgesics, 27%; or ergot derivatives, 16%) and the second with rizatriptan 10-mg wafer. Patients recorded pain intensity and functional disability at the start, and functional disability at 2 hours, as well as the time of return to normal function. RESULTS: A total of 1353 patients, 76% of them female, completed the study and were considered evaluable. During first and second migraine attacks, 55% and 63% of patients, respectively, reported severe disability or requiring bed rest. At 2 hours after treatment, the likelihood of experiencing any disability was more than five times greater after usual nontriptan therapy than after rizatriptan (odds ratio, 5.68; 95% confidence interval (CI), 4.66 to 6.94; P < .001). Rizatriptan was twice as likely to return patients to normal function than usual nontriptan therapy after adjusting for confounding factors (adjusted hazard ratio, 2.08; 95% CI, 1.92 to 2.25; P < .001). Assessed over all time points up to 6 hours, the speed of return to normal function was 52% faster after rizatriptan therapy (P < .001). Significantly more patients preferred rizatriptan than usual nontriptan therapy (78.8% vs. 21.2%; P < .001). The most common reasons cited for preference for rizatriptan were faster relief of headache pain and faster return to normal function. CONCLUSIONS: Patients in this study were more likely to experience a return to normal function at 2 hours after receiving rizatriptan than after their usual nontriptan therapy for migraine. The results of this study, using patient-oriented, clinically relevant endpoints such as functional disability and preference, will help to guide practitioners in making recommendations for acute migraine treatment.

Pradel, F. G., P. Subedi, et al. (2006). "Does earlier headache response equate to earlier return to functioning in patients suffering from migraine?" Cephalalgia **26**(4): 428-35.

This study explored the association between headache response and return to functioning, and identified migraine-associated symptoms related to functional status and acceptability of migraine treatment as reported by patients. Data from migraineurs enrolled in the active arms of a randomized, double-blind, parallel group, placebo-controlled, clinical trial were analysed. The relationships between headache response and functional response, and clinical factors and treatment acceptability were assessed using chi(2) tests of proportions and logistic regressions. A greater proportion of patients with headache response at 0.5 h were functioning at 0.5, 1 and 2 h compared with patients who did not attain a headache response at 0.5 h (P < 0.0001). These

patients also were more likely to find their treatment acceptable ($P < 0.05$). The results suggest a direct temporal relationship among the key determinants of migraine resolution. Rapid headache response is associated with faster return to functioning; rapid headache and functional responses are significant attributes of treatment acceptability.

Tepper, S. J., R. Cady, et al. (2006). "Oral sumatriptan for the acute treatment of probable migraine: first randomized, controlled study." Headache **46**(1): 115-24.

OBJECTIVE: To evaluate the efficacy and tolerability of sumatriptan tablets in adults who meet International Headache Society (IHS) criteria for probable migraine but who do not meet IHS criteria for migraine with or without aura. BACKGROUND: Headaches with some but not all of the features of migraine meet criteria for probable migraine, a form of migraine recognized by the IHS. Probable migraine attacks are also prevalent and frequently underdiagnosed. METHODS: This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. Adults (18 to 65 years) with a 1-year history of headaches that met 2004 IHS criteria for probable migraine without aura (same operational definition as 1988 IHS migrainous disorder) were eligible for enrollment. All patients were triptan- and ergot-naive and had never been diagnosed with migraine. Patients were randomized in a 1:1:1:1 fashion to receive sumatriptan 25, 50, or 100 mg conventional tablets or matching placebo and were instructed to treat a single moderate or severe probable migraine attack. A post hoc analysis was conducted to evaluate the population of patients who achieved headache relief sustained throughout the immediate posttreatment period. Patients who reported relief within 2 hours and subsequently lost headache relief within 4 hours were considered nonresponders. RESULTS: At 2 hours, more patients treated with sumatriptan achieved headache relief, the primary efficacy measure, compared with placebo, but differences only approached statistical significance for 100 mg ($P= .053$). The 2-hour headache relief rate in the sumatriptan 25 or 50 mg groups was not significantly different than placebo. The time to use of rescue was significantly shorter in the placebo group compared with the sumatriptan 100 mg group ($P= .002$). The time to use of rescue in the sumatriptan 25 or 50 mg groups was not significantly different than placebo. More patients treated with placebo (22%) lost headache relief within 4 hours compared with patients treated with sumatriptan 25 mg (17%), 50 mg (14%), or 100 mg (7%). A post hoc analysis demonstrated that at 2 hours, headache relief sustained through 4 hours (S 0-4 hours) was achieved in 44%, 49%, and 57% of patients treated with sumatriptan 25, 50, and 100 mg, respectively, compared with 34% of patients treated with placebo ($P < .05$ for sumatriptan 50 and 100 mg vs. placebo). All doses of sumatriptan were well tolerated and no serious adverse events were reported. CONCLUSION: These results suggest that oral sumatriptan may be effective and is well tolerated for the acute treatment of probable migraine without aura, however, the difference between sumatriptan and placebo was not statistically significant for the a priori defined primary endpoint.

Wendt, J., R. Cady, et al. (2006). "A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults." Clinical Therapeutics **28**(4): 517-26.

OBJECTIVE: The aim of this study was to evaluate the efficacy and tolerability of a single 4-mg dose of sumatriptan SC for the acute treatment of adult patients experiencing a migraine attack with moderate to severe pain. METHODS: In this randomized, double-blind, placebo-controlled study, subjects included men and women aged 18 to 60 years who had migraine with or without aura, as defined by the 1988 International Headache Society criteria. Subjects received either sumatriptan 4 mg SC or placebo SC for a migraine attack with headache pain of moderate to severe intensity. The primary efficacy measurement was pain relief at 2 hours. Secondary efficacy measures included the severity of headache pain at 10, 20, 30, 40, 50, 60, and 90 minutes postadministration. Clinical assessments of pain severity and adverse events were made by way of questioning and observation of subjects and were completed at 10, 20, 30, 40, 50, 60, 90, and

120 minutes postadministration. RESULTS: Five hundred seventy-seven subjects (87% female and 94% white) participated in this study. Three hundred eighty-four received sumatriptan and 193 received placebo. At 120 minutes postadministration, sumatriptan 4 mg SC was associated with greater proportions of patients who experienced pain relief (70% vs 22%; P<0.001) or were pain free (50% vs 11%; P<0.001). In addition, there were statistically significant differences between sumatriptan 4 mg SC and placebo for multiple secondary end points, including pain relief as early as 10 minutes postadministration (11% vs 6%; P=0.039), pain-free status as early as 30 minutes postadministration (10% vs 3%; P<0.001), nausea as early as 30 minutes postadministration (39% vs 49%; P=0.021), and photophobia as early as 10 minutes postadministration (80% vs 87%; P=0.046). The most common adverse events in the sumatriptan 4-mg SC and placebo groups, respectively, were injection-site reactions (43% and 15%), tingling (12% and 3%), dizziness or vertigo (10% and 5%), and warm or hot sensation (8% and 2%). Treatment groups were not statistically compared for adverse events. CONCLUSIONS: Sumatriptan 4 mg SC was effective for the acute treatment of migraine attacks and was generally well tolerated in these patients.

Winner, P., J. Adelman, et al. (2006). "Efficacy and tolerability of sumatriptan injection for the treatment of morning migraine: two multicenter, prospective, randomized, double-blind, controlled studies in adults." Clinical Therapeutics **28**(10): 1582-91.

OBJECTIVE: The aim of this study was to assess the efficacy and tolerability of sumatriptan injection in the treatment of morning migraine. METHODS: In 2 multicenter (20 sites for study 1 and 25 sites for study 2), randomized, double-blind, controlled, parallel-group studies, male and female patients aged 18 to 65 years with migraine meeting International Headache Society criteria received SC sumatriptan succinate injection 6 mg or inactive vehicle (control) for the outpatient treatment of a single morning migraine, defined as migraine with moderate or severe pain on awakening. The primary end point was the percentage of patients who achieved pain-free relief (moderate or severe pain reduced to no pain) at 2 hours after treatment. Tolerability was assessed using spontaneous reporting or noted by a clinician during the studies, assessed at the return visit. RESULTS: The efficacy analysis included, in the succinate group, 145 patients in study 1, 148 in study 2; control, 152 in study 1, 139 in study 2. The mean (SD) ages in the sumatriptan group were 40.2 (9.7) and 38.8 (10.1) years in studies 1 and 2, respectively; control, 41.4 (10.4) and 39.3 (9.7) years. The majority of patients in the 2 studies were female (sumatriptan, 84% and 93% in studies 1 and 2, respectively; control, 82% and 81%) and white (sumatriptan, 83% and 81%; control, 78% and 89%). Two hours after treatment, 48% and 57% of patients treated with sumatriptan injection compared with 18% and 19% of control patients reported pain-free relief in studies 1 and 2, respectively (both, P < 0.001). Two hours after treatment, 72% and 77% of patients treated with sumatriptan injection reported headache relief (moderate or severe pain reduced to mild or no pain) compared with 32% and 41% of control patients (both, P < 0.001). Onset of efficacy versus control (the first time point with statistical significance of pain relief) was observed beginning 10 minutes postdose (P < 0.05 sumatriptan injection vs placebo across pooled studies). Mean time to efficacy in the sumatriptan group was 10 minutes (P < 0.05 vs controls). The most commonly reported adverse events were nausea (sumatriptan, 6% and 4%; control, 2% and 2%) and injection-site reaction (ie, burning or stinging at the injection site) (sumatriptan, 5 % and 5%; control, 2% and 1%). Injection-site reaction was also the only adverse event considered treatment related and reported in > or =5 % of all patients. CONCLUSION: The results of these 2 randomized, double-blind, controlled studies suggest that sumatriptan injection was effective and well tolerated in the acute treatment of morning migraine in these adults.